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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Gregory A. Kopia et. al.		
Serial No.:	09/575,480	Art Unit:	3743
Filed :	May 19, 2000	Examiner:	K.P. ODLAND
For :	DRUG COMBINATIONS USEFUL FOR PREVENTION OF RESTENOSIS		

APPELLANT'S BRIEF ON APPEAL

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The following represents Appellant's Brief on Appeal in the above-captioned application:

I. REAL PARTY OF INTEREST

The real party of interest of the present application on appeal is the assignee, Cordis Corporation.

II. RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences known to appellant's legal representative or assignee, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1, 3 – 4, 6, and 8 – 9 are pending in this application and have been finally rejected in this application by means of a final rejection dated June 2, 2004. Claims 2, 5, 7, and 10 – 15 were cancelled without prejudice during prosecution. Each of Claims 1, 3 – 4, 6, and 8 – 9 are on appeal.

IV. STATUS OF AMENDMENTS

A Response after Final Rejection was deposited with the United States Postal Service on September 2, 2004 in response to the Final Rejection dated June 2, 2004. In an Advisory Action mailed on October 19, 2004, the Examiner indicated that the Response after Final Rejection failed to place the application in condition for allowance. Nonetheless, the Examiner entered the claim amendments made in the Response after Final Rejection.

IV. SUMMARY OF INVENTION

The invention embodied by the subject application on appeal is directed to an approach to solving the clinical problem of restenosis, which involves the administration of drug combinations, either locally or systemically. One example of such a combination would be the addition of the anti-inflammatory corticosteroid, dexamethasone, with an antiproliferative agent such as rapamycin or its analogues. Delivery of a stent containing both an ***antiproliferative agent and an anti-inflammatory agent*** *(emphasis added)* to a coronary artery injured during the process of angioplasty would provide the added therapeutic benefit of:

1. Limiting the degree of local smooth muscle cell proliferation;
2. Reducing a stimulus for proliferation, i.e., inflammation, and thus enhance the restenosis-limiting action of the stent.

An additional benefit of combination drug therapy may be to reduce the dose of each of the therapeutic components and thus limiting their toxicity, while still achieving a reduction in restenosis. See Table 1 (included below), which demonstrates that concentrations of rapamycin or dexamethasone below their respective IC_{50} amounts may combine to produce an effect on cell growth greater than either agent individually.

% of Control Growth	Concentration of Dexamethasone									
	0	0.01	0.05	0.1	0.5	1.0	5.0	10	50	100
Rapamycin 0 ug/ml	100.0	-	-	75.2	76.5	72.2	50.0	36.1	18.3	11.7
Standard Deviation	4.2			0.8	16.3	9.3	7.6	5.9	6.0	1.3
Rapamycin 0.2 ug/ml	85.7	63.4	57.6	49.7	48.9	48.2	41.2	31.1	31.2	29.0
Standard Deviation	6.6	3.2	2.1	4.6	2.2	1.7	3.0	2.7	1.0	1.8
Rapamycin 1.0 ug/ml	67.4	48.3	45.1	38.1	39.2	37.8	33.9	25.8	20.7	18.5
Standard Deviation	2.6	3.3	13.3	9.5	4.4	4.5	3.1	8.1	6.4	3.7

Table 1: Inhibition of human vascular smooth muscle cell proliferation with dexamethasone or dexamethasone + rapamycin.

Further aspects of this summary are seen in the specification at page 8, lines 7-23, page 10, lines 14-28, page 11, lines 11-15, and page 13, lines 11-20.

V. ISSUES[1]

1. Is Claim 1 patentable in light of 35 U.S.C. §112?
2. Are Claims 1, 3, 4, and 6 patentable under 35 U.S.C. §102 in view of U.S. Patent No. 6,335,029 to Kamath?
3. Are Claims 8-9 patentable under 35 U.S.C. §103 over U.S. Patent No. 6,335,029 to Kamath in view of U.S. Patent No. 6,159,488 to Nagler?

VI. ARGUMENT

1. Is Claim 1 patentable in light of 35 U.S.C. §112?

Claim 1 is patentable in light of 35 U.S.C. §112. As amended, claim 1 now satisfies all of the requirements 35 U.S.C. §112. The Examiner originally rejected claim 1 under 35 U.S.C. §112 for lack of antecedent basis for the term "said layers." As noted in applicant's response dated September 2, 2004, an inadvertent typographical error inserted the word "layers" for the word "agents." The term "said agents" now has antecedent support in amended claim 1, thus making the claim reasonably ascertainable by those skilled in the art. [*Ex parte Porter*, 25 USPQ2d 1144, 1145 (Bd. Pat. App. & Inter. 1992)]

2. Are Claims 1, 3, 4, and 6 patentable under 35 U.S.C. §102 in view of U.S. Patent No. 6,335,029 to Kamath?

Claims 1, 3, 4, and 6 are patentable under 35 U.S.C. §102 over U.S. Patent No. 6,335,029 to Kamath, et. al. The Examiner has rejected Claim 1 under 35 U.S.C. §102, citing Kamath. In so doing, the Examiner has characterized the drug Taxol as a rapamycin "analogue." Applicants respectfully contend that this is an improper characterization.

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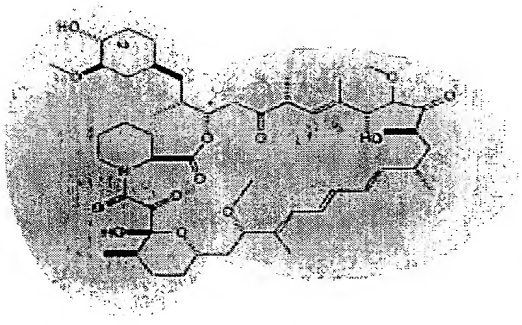
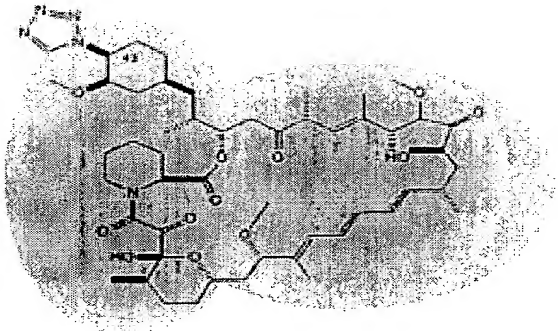
[1] Appellants note that there is a provisional obviousness-type double patenting rejection along with co-pending application 09/850,482. However, the allegedly conflicting claims of the co-pending application have not been patented. As such, assuming a successful showing to the Board, appellants respectfully request that this provisional rejection be removed.

Taxol is formed from the compound paclitaxel. While both rapamycin and paclitaxel may exhibit antiproliferative properties, these two drugs are different in both their chemical structure and method of action. The attached drawings show the chemical structure of both rapamycin and paclitaxel. Upon a review of the images, one can see clearly that the chemical structures of these compounds share little in common. In this regard, one could not characterize the two families of drugs as "analogues." In contrast, each pair of the true "analogues" (for instance, rapamycin and its analogue, ABT-578, or taxol and its analogue, docetaxel) has very similar structures. As well, both pairs of true analogues have similar methods of action.

Chemical Structure - Rapamycin and a Rapamycin Analogue:

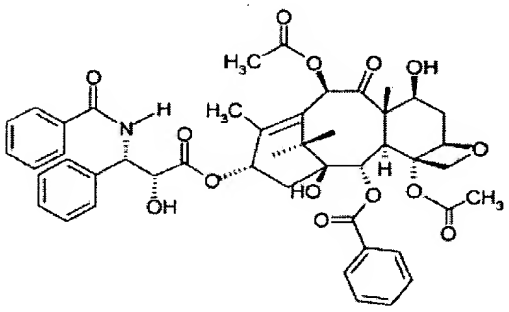


Rapamycin

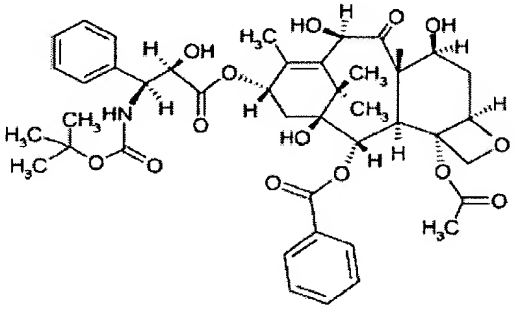


ABT-578 (A Rapamycin Analogue)

Chemical Structure - Taxol and a Taxol Analogue:



Paclitaxel (Taxol)



Docetaxel (A Paclitaxel Analogue)

The method of action of these two classes of drugs is quite different. Paclitaxel is a drug originally formulated for cancer therapy, since it interferes with the growth of cancer cells, which are eventually destroyed. Essentially, paclitaxel causes cells to experience programmed cell death without dividing. Rapamycin, also known as sirolimus was formulated as an immunosuppressive agents to prevent tissue rejection during transplant surgery. Sirolimus works to prevent the white blood cells from getting rid of the transplanted organ, and in so doing exhibits cytostatic properties.

The Examiner's argument is misplaced that, because applicant originally submitted claims pairing rapamycin with taxol and vincristine in a *Markush* grouping[2], the agents cited are "analogues." A *Markush* grouping is a homegrown generic expression covering a group of two or more different materials, any one of which will be operative for the combination claimed. Applicant submits that, to extrapolate that the elements of a *Markush* grouping, are necessarily *analogues* as used in the drug sense, is entirely inappropriate. Moreover, without a clear showing made by the Examiner that the drugs function as analogues, any argument based on inherency of the drugs' properties is certainly inappropriate, given appellants clear showing of the different modes of operation.

Examiner makes the additional argument that the dictionary meaning of "analogue" is defined as a structure that is similar in function to one in another according to The American Heritage® Dictionary. However, the pharmaceutical sense, "analogue" has a more specific meaning specifically, "a chemical compound with a structure similar to that of another but differing from it in respect to a certain component."[3] Under this definition, clearly taxol is not a rapamycin "analogue."

Since appellants have shown that taxol is not a rapamycin analogue, and Kamath does not disclose a rapamycin or a rapamycin analogue, the rejection in light of Kamath is inappropriate.

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[2] See Claim 9.
[3] Dorland's Medical Dictionary, pg. 66 (26th ed. 1981).

3. Are Claims 8-9 patentable under 35 U.S.C. §103 over U.S. Patent No. 6,335,029 to Kamath in view of U.S. Patent No. 6,159,488 to Nagler?

Claims 8 and 9 are patentable under 35 U.S.C. §103 over Kamath in view of U.S. Patent No. 6,159,488 to Nagler, *et al.* It has already been shown herein that taxol is not a rapamycin analogue. In this regard, Kamath in view of Nagler does not teach or suggest each of the claim limitations, specifically the use of an antiproliferative "comprising rapamycin or an analogue thereof..."

The examiner states that the Kamath reference discloses the invention as applied to Claim 1 but fails to recite halofuginone as an extracellular matrix inhibitor. The examiner further cites the Nagler reference to teach a stent coated with halofuginone, and then states it would be obvious to one with ordinary skill in the art to modify Kamath to include halofuginone. "When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine said references." *In re Rouffet,* 149 F.3d 1350, 1355 (Fed Cir. 1998). There is no such suggestion or motivation in either reference to combine the cited references. The Examiner has shown no suggestion or motivation to combine, and the references themselves do not imply a reason to combine these references. Furthermore, Kamath simply *does not teach* the use of an antiproliferative comprising rapamycin or an analogue thereof.

Given that Kamath falls short as a 35 USC §102 reference as it relates to the claimed invention, it also falls short as a 35 USC §103 reference as applied herein. In this regard, claims 8 and 9 are patentable under 35 U.S.C. §103.

VII. SUMMARY

Appellants submit that the above remarks and supporting information establish that the Examiner's cited grounds for rejection are improper and as such should be reversed. Appellant thus respectfully requests that the Board of Patent Appeals and Interferences find that the remaining claims are in condition for allowance, with instructions to the Examiner to allow the claims.

Respectfully submitted,

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APPENDIX

1. (Previously Amended) A method for treating restenosis comprising an intravascular infusion or delivery by release from a surface of a stent of a combination of at least two agents, including an anti-proliferative agent for inhibiting smooth muscle cell growth comprising rapamycin or an analogue thereof and an anti-inflammatory agent for inhibiting smooth muscle growth, both said agents contained in therapeutic dosage amounts.

3. (Previously Amended) The method of claim 1 wherein the anti-inflammatory agent comprises dexamethasone.

4. (Previously Amended) The method of claim 1 wherein the combination of at least two agents further includes a growth factor or cytokine signal transduction inhibitor.

5. (Canceled)

6. (Previously Amended) The method of claim 1 wherein the combination of at least two agents further includes a tyrosine kinase inhibitor.

7. (Canceled)

8. (Previously Amended) The method of claim 1 wherein the combination of at least two agents further includes an inhibitor of extracellular matrix synthesis.

9. (Previously Amended) The method of claim 8 wherein the inhibitor of extracellular matrix synthesis comprises halofuginone and the anti-proliferative agent is taken from a group consisting of rapamycin, taxol, or vincristine.

10. (Canceled)

11. (Canceled)

12. (Canceled)

13. (Canceled)

14. (Canceled)

15. (Canceled)